

Figure 1A

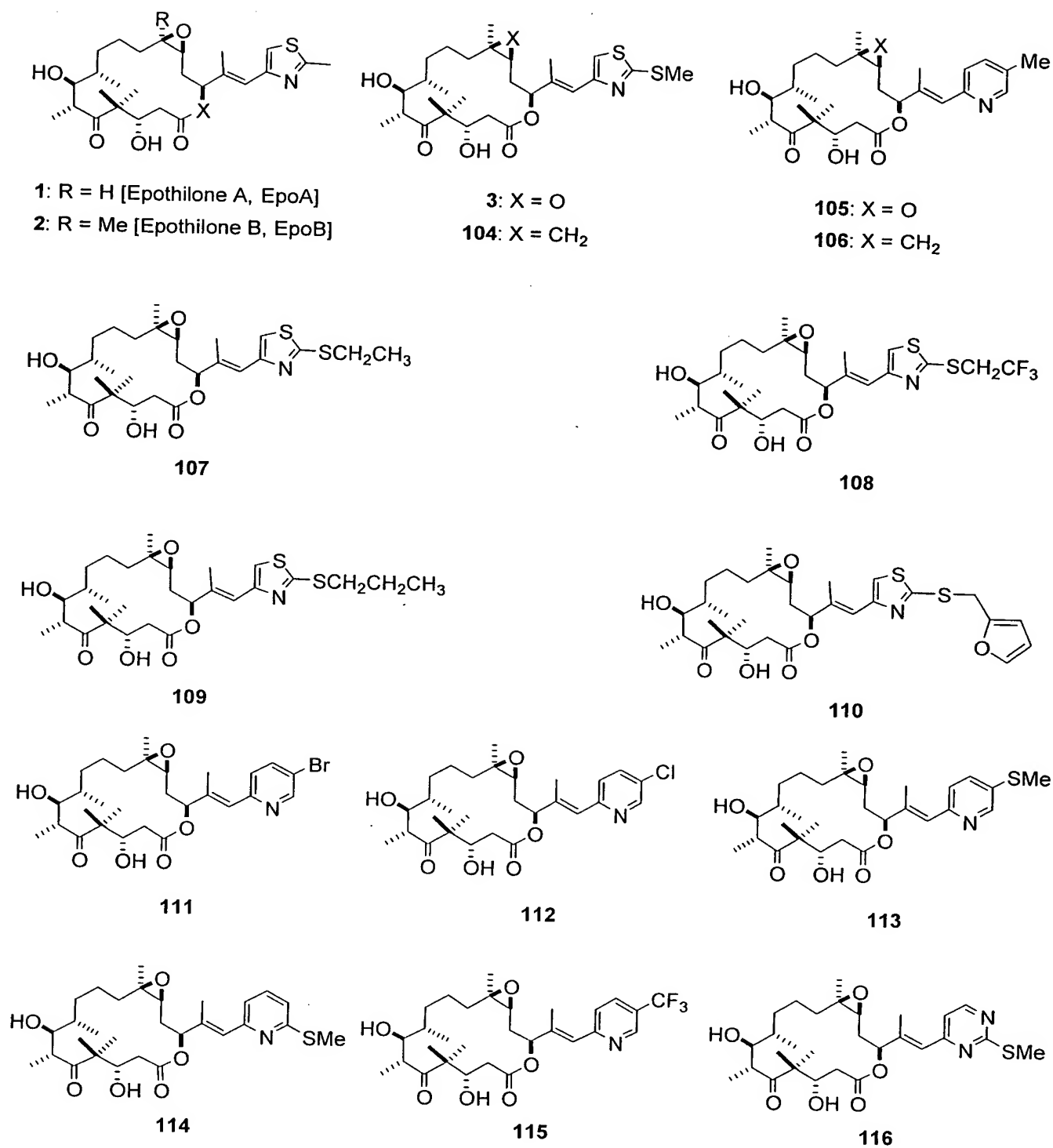


Figure 1B

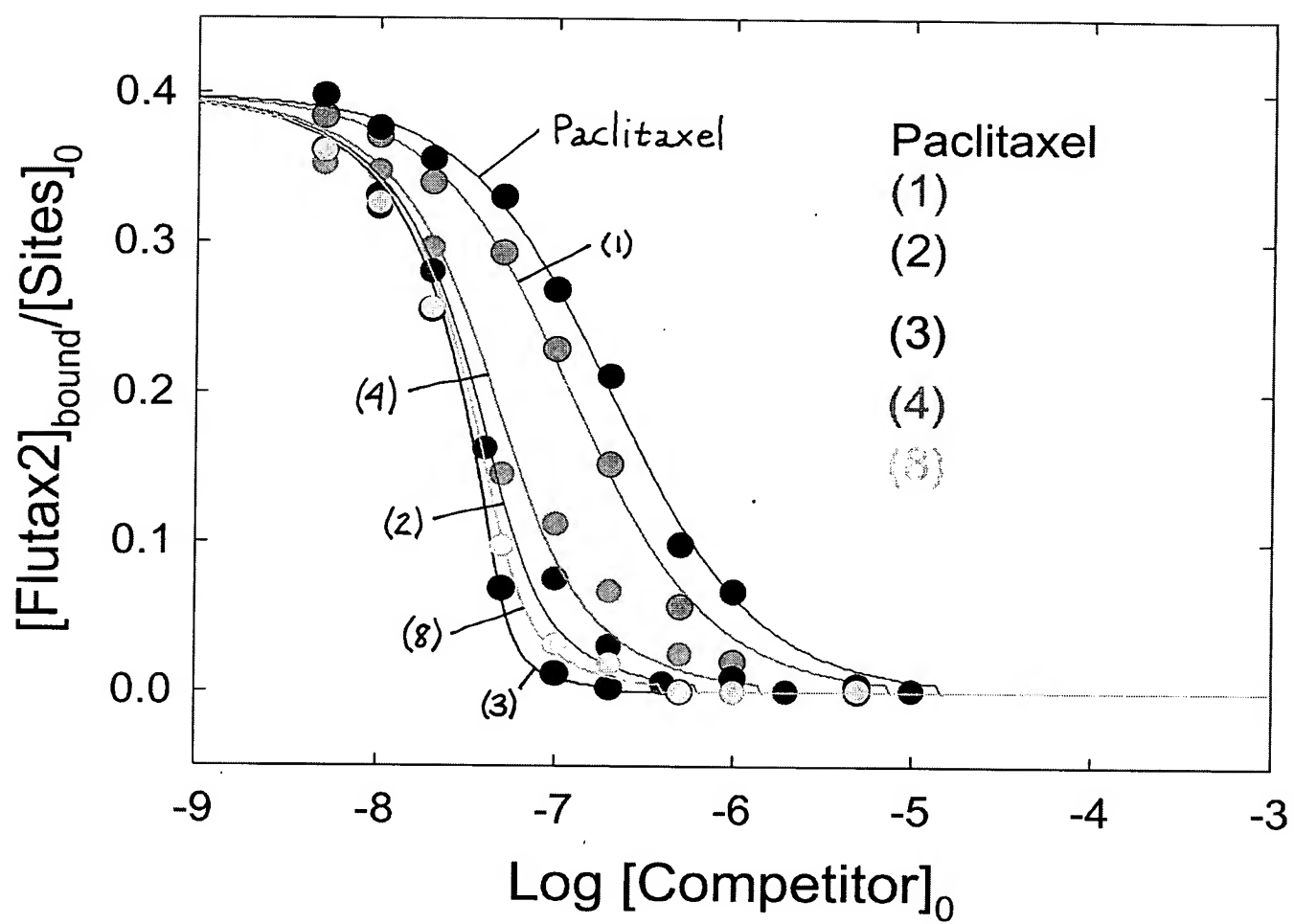


FIGURE 2

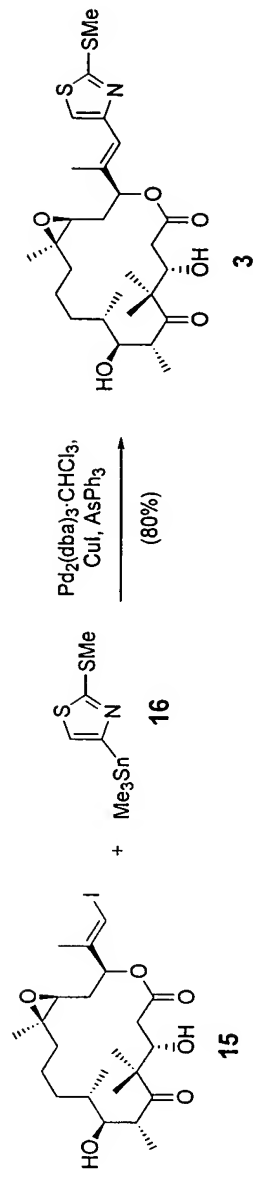


Figure 3

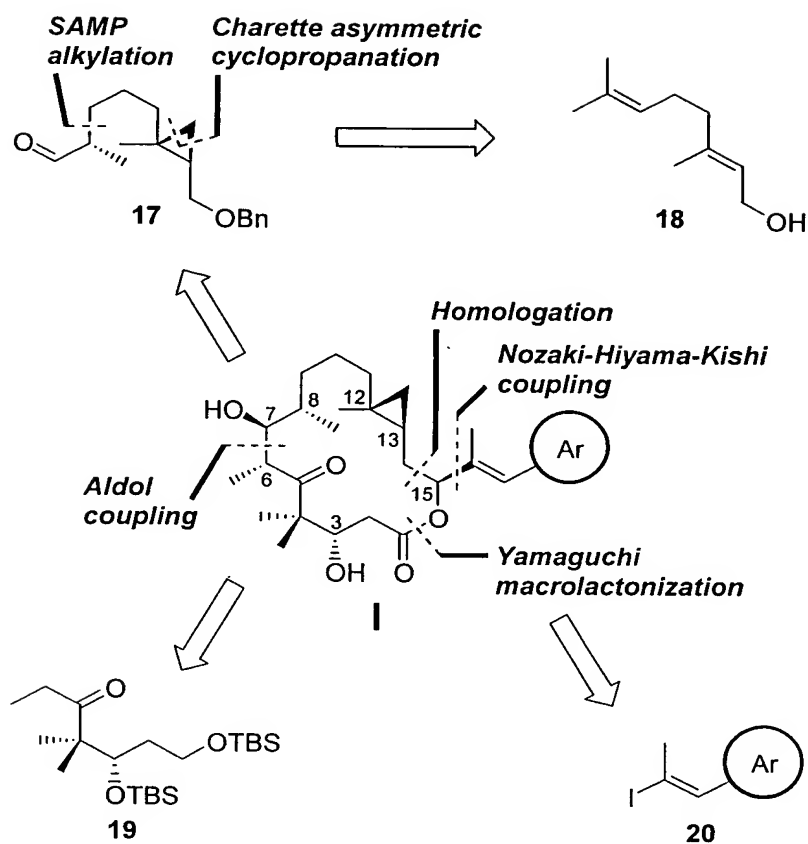


Figure 4

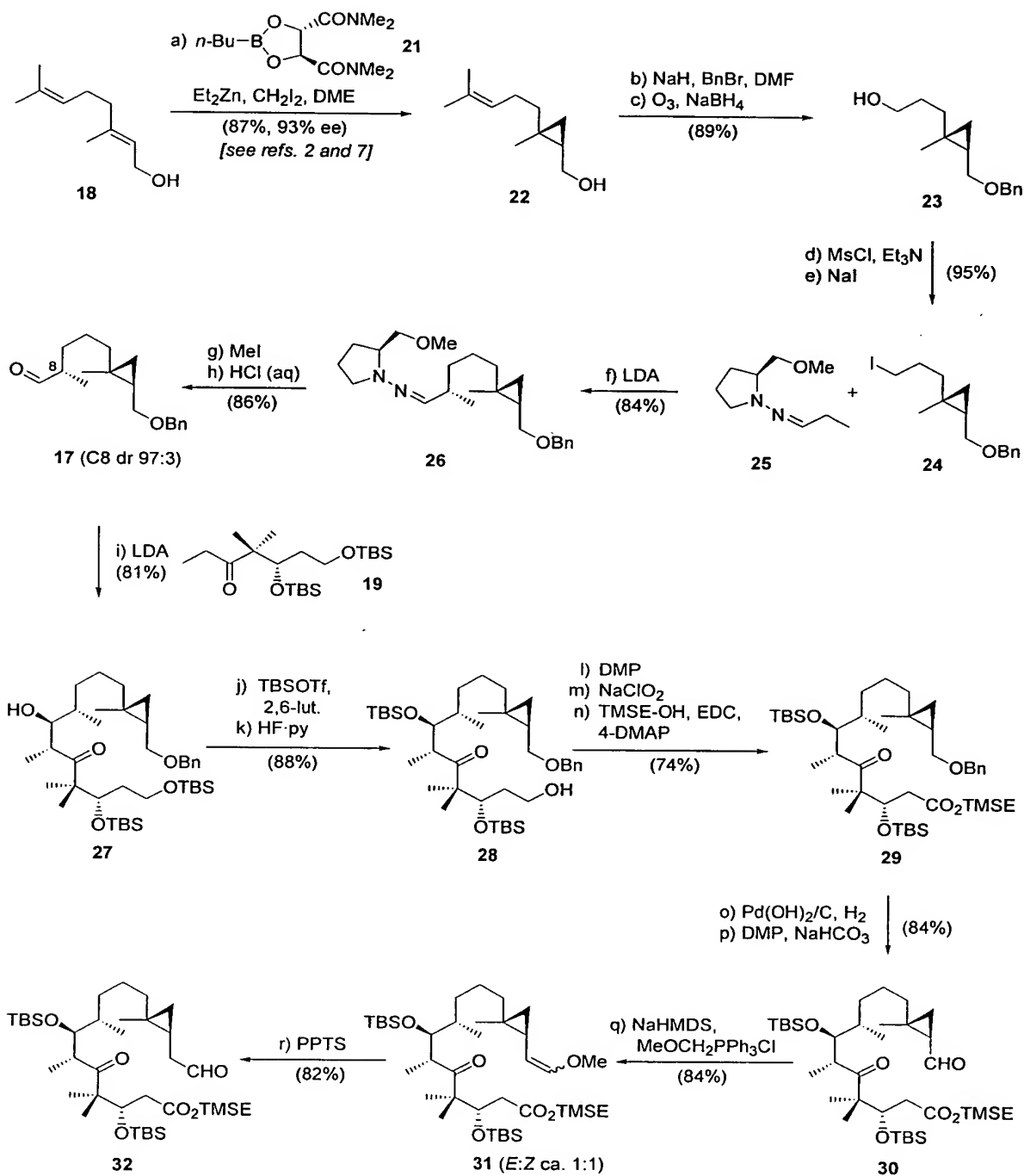


Figure 5

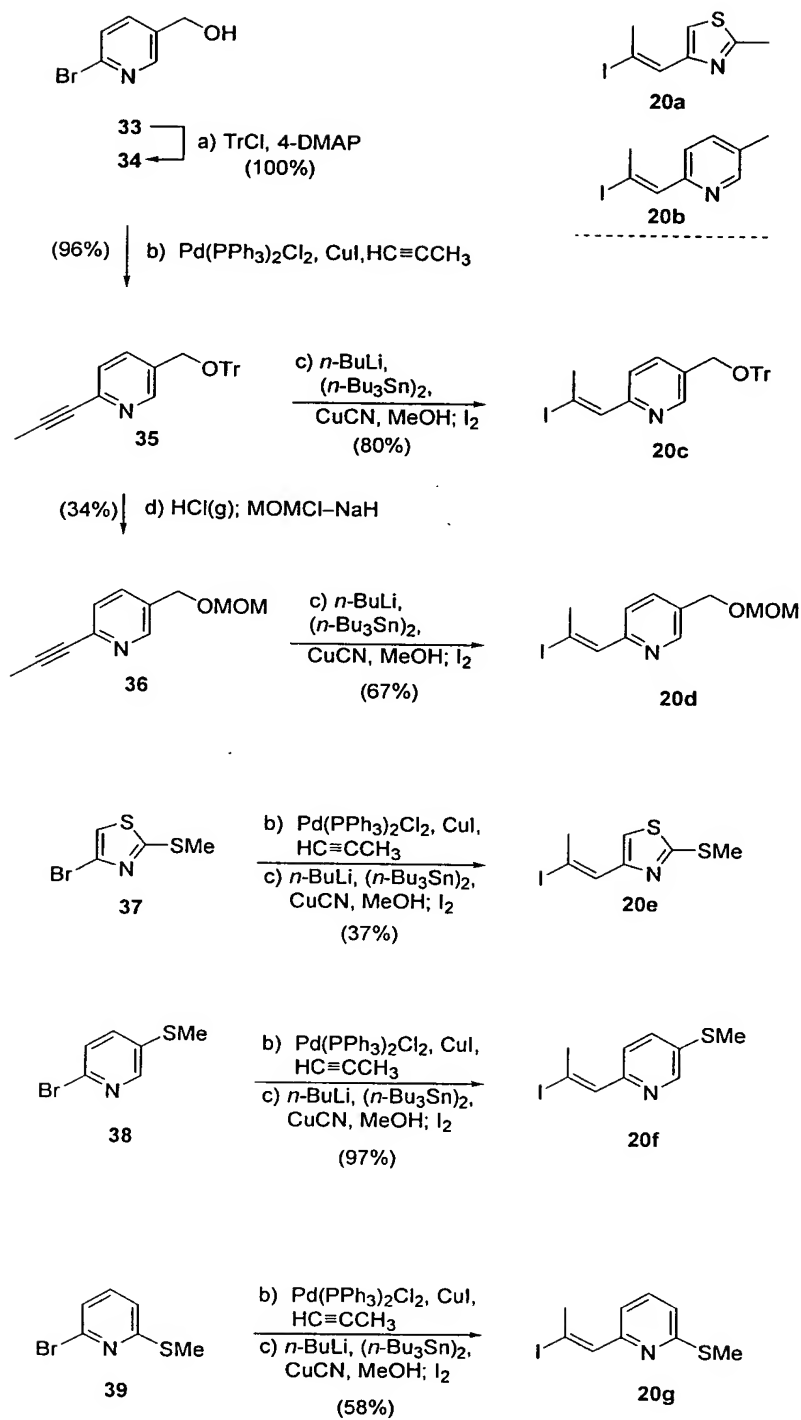
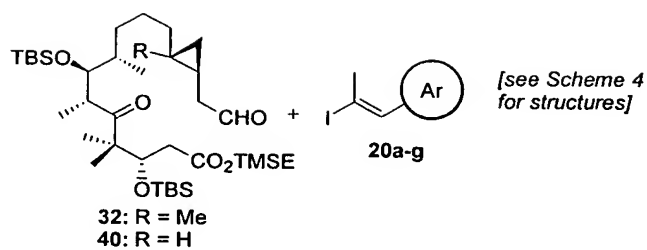
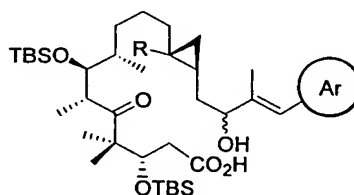


Figure 6

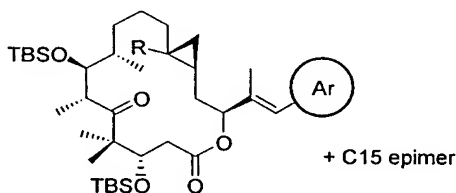


a) CrCl_2 , NiCl_2 , 4-*t*-Bu-py
 b) TBAF



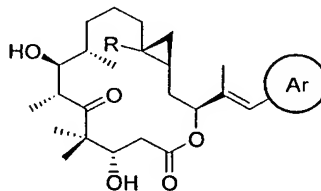
| Entry | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|-----------|-----|-----|-----|-----|-----|-----|-----|-----|
| Compound | 41a | 41b | 41d | 41e | 41f | 41g | 42c | 42e |
| R | Me | Me | Me | Me | Me | Me | H | H |
| Yield (%) | 73 | 57 | 49 | 62 | 63 | 46 | 46 | 39 |

c) Et_3N , 2,4,6-trichlorobenzoyl-chloride, 4-DMAP



| Entry | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|-----------|-----|-----|-----|-----------------|-----|-----|-----|-----|
| Compound | 43a | 43b | 43d | 43e | 43f | 43g | 44c | 44e |
| R | Me | Me | Me | Me | Me | Me | H | H |
| Yield (%) | 33 | 28 | 35 | 35 ^g | 35 | 37 | 33 | 47 |

d) 20% TFA in CH_2Cl_2



| Entry | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|-----------|----|----|----|----|----|----|----|----|
| Compound | 6 | 8 | 10 | 12 | 13 | 14 | 9 | 11 |
| R | Me | Me | Me | Me | Me | Me | H | H |
| Yield (%) | 73 | 48 | 56 | 49 | 68 | 48 | 54 | 68 |

Figure 7

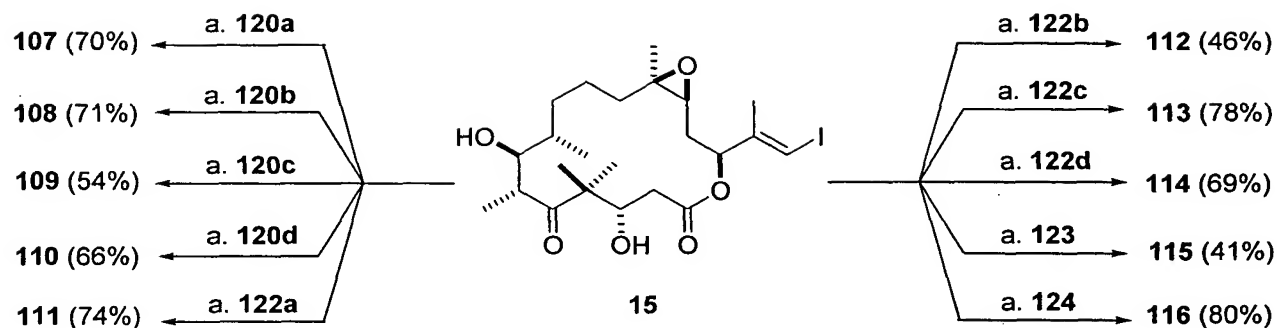


Figure 8

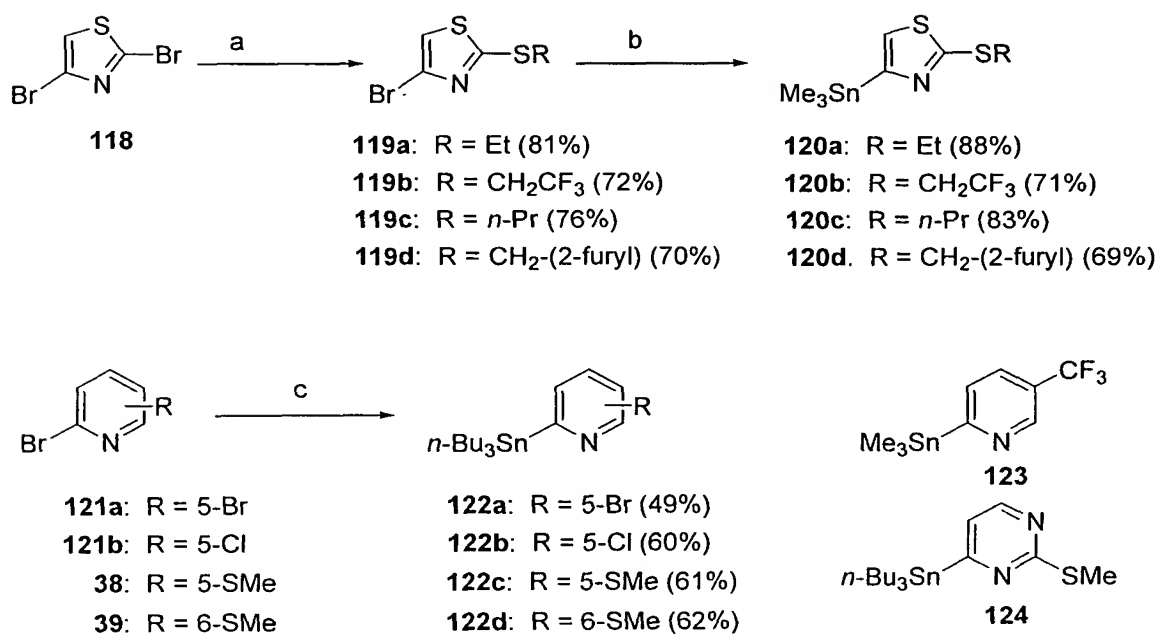


Figure 9

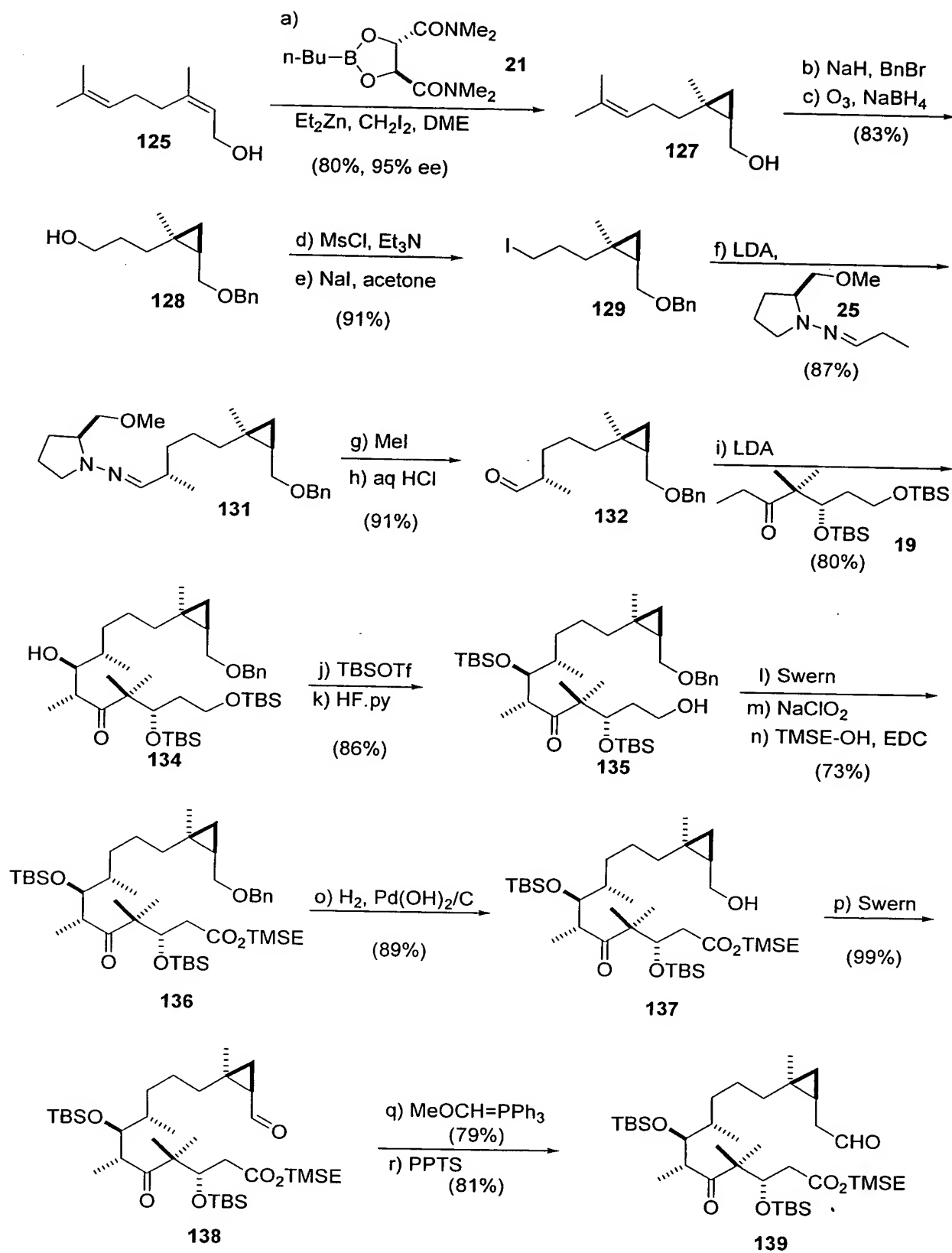


Figure 10

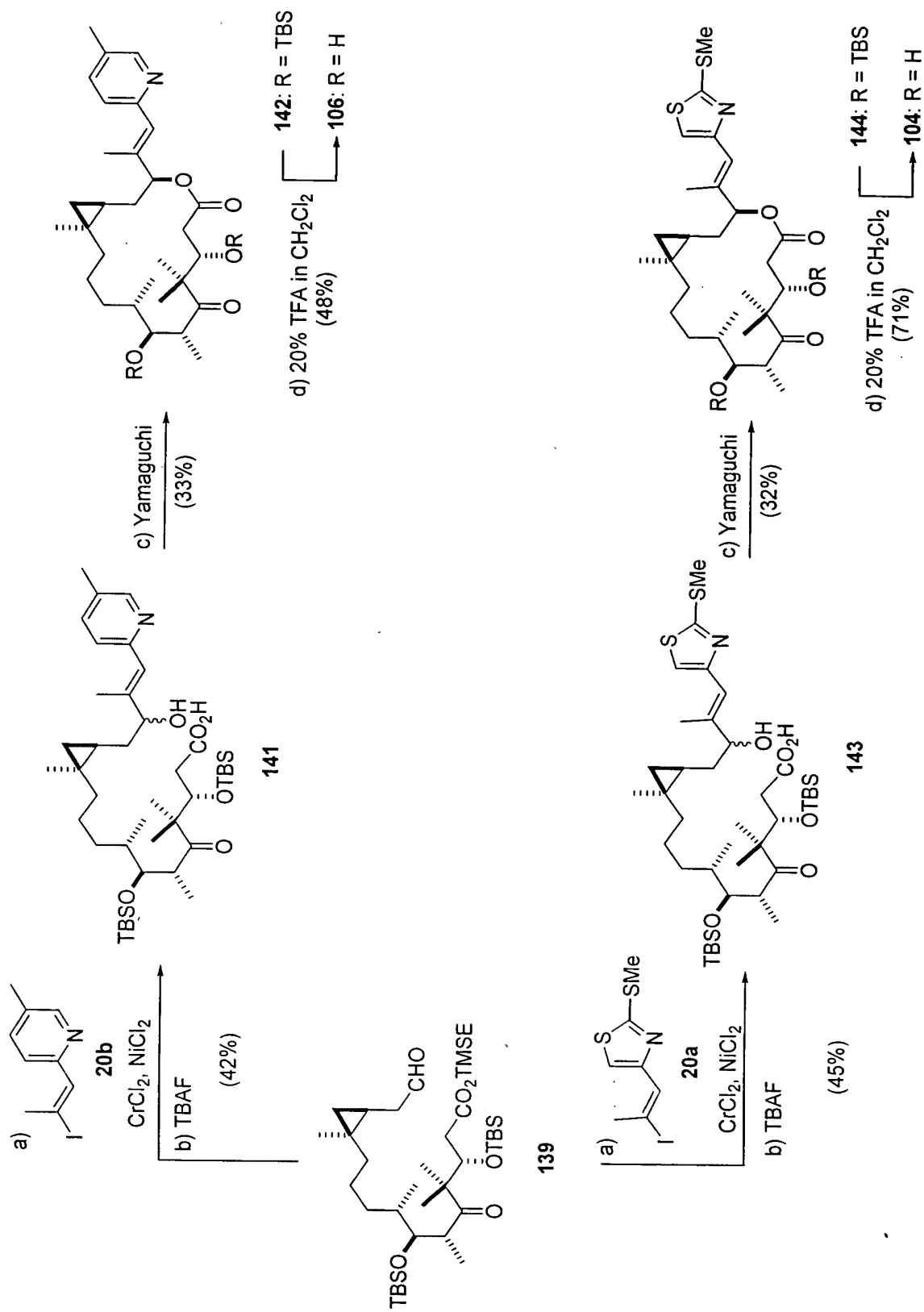


Figure 11

| Compound | Cell Line | | | | | |
|---------------------|-----------------------|------|-----------------------|------|-----------------------|------|
| | 1A9 | | A8 | | PTX10 | |
| | IC ₅₀ (nM) | RR | IC ₅₀ (nM) | RR | IC ₅₀ (nM) | RR |
| Taxol TM | 3.0 ± 0.4 | 3.3 | 10.1 ± 2.9 | 3.3 | 89.7 ± 9.0 | 29.5 |
| Epo A | 2.4 ± 0.6 | 38.7 | 91.0 ± 10.0 | 38.7 | 34.2 ± 2.0 | 14.5 |
| Epo B | 0.6 ± 0.3 | 10.7 | 6.5 ± 0.9 | 10.7 | 3.1 ± 0.5 | 5.2 |
| 3 | 0.17 ± 0.8 | 7.6 | 1.3 ± 0.65 | 7.6 | 0.26 ± 0.11 | 1.5 |
| 104 | 0.1 ± 0.0 | 23.5 | 2.4 ± 1.1 | 23.5 | 0.7 ± 0.3 | 6.5 |
| 106 | 0.3 ± 0.1 | 41.4 | 10.4 ± 2.4 | 41.4 | 3.3 ± 1.2 | 13.2 |
| 108 | 3.5 ± 0.7 | 5.3 | 18.4 ± 1.4 | 5.3 | 16.1 ± 2.1 | 4.6 |
| 109 | 4.4 ± 2.4 | 9.7 | 42.9 ± 5.1 | 9.7 | 24.7 ± 4.9 | 5.6 |
| 110 | 2.1 ± 0.8 | 7.6 | 16.0 ± 5.5 | 7.6 | 9.8 ± 1.4 | 4.7 |
| 111 | 0.7 ± 0.2 | 16.6 | 11.1 ± 1.0 | 16.6 | 3.9 ± 0.4 | 5.8 |
| 112 | 3.2 ± 0.1 | 10.0 | 31.9 ± 3.1 | 10.0 | 16.1 ± 4.1 | 5.1 |
| 113 | 0.4 ± 0.1 | 31.7 | 11.6 ± 6.7 | 31.7 | 3.9 ± 1.1 | 10.5 |
| 114 | 3.3 ± 0.2 | 8.3 | 27.7 ± 3.2 | 8.3 | 12.2 ± 7.4 | 3.7 |
| 115 | 4.3 ± 0.4 | 19.2 | 83.0 ± 2.0 | 19.2 | 65.3 ± 11.9 | 15.1 |
| 116 | 8.6 ± 1.2 | 3.8 | 32.3 ± 2.7 | 3.8 | 42.9 ± 10.3 | 5.0 |
| | | | | | IC ₅₀ (nM) | RR |
| | | | | | 53.4 ± 26.5 | 17.6 |
| | | | | | 8.7 ± 2.2 | 3.7 |
| | | | | | 0.8 ± 0.5 | 1.3 |
| | | | | | 0.25 ± 0.17 | 1.5 |
| | | | | | 0.6 ± 0.5 | 5.9 |
| | | | | | 1.3 ± 1.1 | 5.3 |
| | | | | | 3.8 ± 0.3 | 1.1 |
| | | | | | 5.2 ± 0.8 | 1.2 |
| | | | | | 2.9 ± 1.3 | 1.4 |
| | | | | | 0.3 ± 0.1 | 0.5 |
| | | | | | 3.2 ± 0.3 | 1.0 |
| | | | | | 2.1 ± 1.9 | 5.8 |
| | | | | | 6.6 ± 2.6 | 2.0 |
| | | | | | 9.6 ± 1.3 | 2.2 |
| | | | | | 9.6 ± 1.0 | 1.1 |

Figure 12

| Compound | Cell Line | KB-31 | KB-8511 |
|----------|-----------|-----------------------|-----------------------|
| | | IC ₅₀ (nM) | IC ₅₀ (nM) |
| Epo B | | 0.19 | 0.12 |
| 3 | | 0.11 | 0.07 |
| 104 | | 0.20 | 0.12 |
| 106 | | 0.44 | 0.29 |
| 108 | | 3.04 | 2.67 |
| 109 | | 10.0 | 6.73 |
| 110 | | 1.16 | 1.28 |
| 111 | | 0.72 | 0.55 |
| 113 | | 0.54 | 0.41 |
| 114 | | 4.87 | 3.24 |
| 115 | | 8.38 | 7.37 |
| 116 | | 9.01 | 11.65 |

Figure 13

Figur 14

| Compound | Cell line | | | | | | |
|-------------------------|------------------|------------------|------|------------------|------|------------------|------|
| | 1A9 | A8 (β274) | | PTX10 (β270) | | PTX22 (β364) | |
| | IC ₅₀ | IC ₅₀ | RR | IC ₅₀ | RR | IC ₅₀ | RR |
| epothilone A (Epo A) 1 | 3.1 ± 0.72 | 77.3 ± 9.25 | 24.9 | 29.1 ± 7.24 | 9.4 | 10.1 ± 2.10 | 3.3 |
| epothilone B (Epo B) 2 | 0.3 ± 0.05 | 6.5 ± 1.70 | 21.7 | 3.7 ± 1.83 | 12.3 | 2.1 ± 1.45 | 7 |
| paclitaxel (Taxol®) | 1.3 ± 0.22 | 11.3 ± 0.83 | 8.7 | 47.7 ± 5.01 | 36.7 | 29.4 ± 3.69 | 22.6 |
| tmt-epo B 3 | 0.17 ± 0.08 | 1.3 ± 0.65 | 7.6 | 0.26 ± 0.11 | 1.5 | 0.25 ± 0.17 | 1.5 |
| cis-CP-py-epo A 4 | 2.4 ± 0.99 | 41.6 ± 8.58 | 17.3 | 19.2 ± 9.39 | 8 | 4.2 ± 2.18 | 1.8 |
| trans-CP-epo A 5 | 10.1 ± 6.59 | 33.9 ± 5.56 | 3.4 | 17.2 ± 5.97 | 1.7 | 4.7 ± 1.68 | 0.5 |
| trans-CP-epo B 6 | 15 | >150 | >10 | 52 | 3.5 | 5 | 0.3 |
| trans-CP-py-epo A 7 | 0.6 ± 0.22 | 10.1 ± 2.07 | 16.8 | 5.9 ± 1.96 | 9.8 | 1.4 ± 0.51 | 2.3 |
| trans-CP-py-epo B 8 | 1.7 ± 0.76 | 27.9 ± 6.73 | 16.4 | 10.9 ± 3.52 | 6.4 | 5.6 ± 3.24 | 3.3 |
| trans-CP-pyOH-epo A 9 | 0.7 ± 0.16 | 13.0 ± 2.17 | 18.6 | 6.1 ± 1.90 | 8.7 | 1.1 ± 0.38 | 1.6 |
| trans-CP-pyOH-epo B 10 | 1.7 ± 1.12 | 13.2 ± 5.02 | 7.8 | 10.2 ± 3.75 | 6 | 2.5 ± 1.41 | 1.5 |
| trans-CP-tmt-epo A 11 | 1.2 ± 0.67 | 11.2 ± 2.30 | 9.3 | 3.2 ± 1.13 | 2.7 | 0.8 ± 0.38 | 0.7 |
| trans-CP-tmt-epo B 12 | 3.5 ± 1.64 | 28.9 ± 8.01 | 8.3 | 5.7 ± 1.96 | 1.6 | 11.5 ± 3.86 | 3.3 |
| trans-CP-5tmpy-epo B 13 | 14.2 ± 5.73 | 94 ± 5 | 6.6 | 72.0 ± 10.41 | 5.1 | 20.6 ± 9.06 | 1.5 |
| trans-CP-6tmpy-epo B 14 | 114 | >150 | >1.3 | >150 | >1.3 | 104 | 0.9 |

Figure 15

| Compound | % TP ^a | KB-31 ^b | KB-8511 ^b | RR |
|--|----------------------|--------------------|----------------------|-------------------|
| epothilone A (Epo A) 1 | 78 | 2.15 ^c | 1.91 ^c | 0.88 ^c |
| epothilone B (Epo B) 2 | 93 | 0.19 ^c | 0.18 ^c | 0.95 ^c |
| paclitaxel (Taxol [®]) | 52 | 2.92 ^c | 626 ^c | 214 ^c |
| Tmt-epo B 3 | 99 | 0.11 | 0.07 | 0.61 |
| <i>cis</i> -CP-py-epo A 4 | 100 ^c | 0.62 ^c | 0.45 ^c | 0.72 ^c |
| <i>trans</i> -CP-epo A 5 | 100 ^c | 0.97 ^c | 0.64 | 0.66 ^c |
| <i>trans</i> -CP-epo B 6 | 82 | 1.84 | 1.09 | 0.59 |
| <i>trans</i> -CP-py-epo A 7 | 94 ^c | 0.84 ^c | 0.68 ^c | 0.81 ^c |
| <i>trans</i> -CP-py-epo B 8 | 89 | 0.90 | 0.61 | 0.68 |
| <i>trans</i> -CP-pyOH-epo B 10 | 87 | 0.44 | 0.55 | 1.25 |
| <i>trans</i> -CP-tmt-epo A 11 | 93 | 0.66 | 0.32 | 0.48 |
| <i>trans</i> -CP-tmt-epo B 12 | 91 | 0.67 | 0.45 | 0.67 |
| <i>trans</i> -CP-5tmpy-epo B 13 | 88 | 6.88 | 5.28 | 0.77 |
| <i>trans</i> -CP-6tmpy-epo B 14 | 58 | 109 | 74 | 0.68 |

Figur 16

| Compound | K_d (37 °C) ^b | ΔG_{app}° (37 °C) ^c |
|--|----------------------------|---|
| epothilone A (Epo A) 1 | 34 ± 4 | -44.5 ± 0.3 |
| epothilone B (Epo B) 2 | 1.6 ± 0.1 | -52.6 ± 0.5 |
| paclitaxel (Taxol®) | 93 ± 26 | -42.2 ± 0.2 |
| tmt-epo B 3 | 0.64 ± 0.24 | -54.5 ± 1.2 |
| <i>cis</i> -CP-py-epo A 4 | 5.2 ± 0.8 | -49.4 ± 0.3 |
| <i>trans</i> -CP-epo A 5 | 6.5 ± 0.1 | -48.6 ± 0.1 |
| <i>trans</i> -CP-epo B 6 | 8.0 ± 1.8 | -48.0 ± 0.1 |
| <i>trans</i> -CP-py-epo A 7 | 2.1 ± 0.4 | -51.5 ± 0.2 |
| <i>trans</i> -CP-py-epo B 8 | 1.9 ± 0.6 | -51.8 ± 0.8 |
| <i>trans</i> -CP-pyOH-epo B 10 | 6.0 ± 0.6 | -48.9 ± 0.3 |
| <i>trans</i> -CP-tmt-epo A 11 | 1.6 ± 0.5 | -52.2 ± 0.9 |
| <i>trans</i> -CP-tmt-epo B 12 | 1.8 ± 0.2 | -51.8 ± 0.3 |
| <i>trans</i> -CP-5tmpy-epo B 13 | 1.9 ± 0.3 | -51.6 ± 0.5 |
| <i>trans</i> -CP-6tmpy-epo B 14 | 53 ± 8 | -43.1 ± 0.5 |